mentally a cellular machinery problem, not a protein problem.

In this new story, α-synuclein is actually a reaction to the root cause of Parkinson’s, Ole Isacson, a neuroscientist at Harvard Medical School, tells The Scientist.

A gut feeling

In 1912, Fritz Heinrich Lewy, a doctor working in Berlin, studied the brains of patients who had died from Parkinson’s disease (then known as shaking palsy) and found odd clumps of proteins in their nerve cells. Several years later, Spanish neurologist Gonzalo Rodríguez Lafuente, who had identified the protein inclusions in the brain of another patient who had died of shaking palsy, dubbed them Lewy bodies.

Based on additional probes into diseased patients’ brains, neurologists found Lewy bodies to be particularly common in the substantia nigra, a brain region that sits in the center of the head directly behind the eyes. It’s where many of the neurons that produce dopamine, a neurotransmitter involved in movement and learning and in regulating mood, originate. These neurons send signals to another brain region called the striatum, forming a neural pathway that facilitates muscle motion; in Parkinson’s disease, it’s the dopamine neurons in the substantia nigra that are damaged or destroyed. People with Parkinson’s typically have trouble with balance and walking, and they often suffer from tremors in the hands or fingers and other involuntary movements.

Laboratory investigations in the 1990s suggested that Lewy bodies were composed of α-synuclein, while early explorations of the genetics of Parkinson’s published around the same time revealed that patients with an inherited form of the disease often carried mutations in the SNCA gene, which encodes α-synuclein. Together, the pathology and genetic findings suggested that α-synuclein might be the pathologic protein underlying Parkinson’s disease, pathologist Kelvin Luk of the Perelman School of Medicine at the University of Pennsylvania tells The Scientist.

In the early 2000s, Goethe University Frankfurt neuroanatomist Heiko Braak built on that work, observing that α-synuclein accumulation didn’t just occur in the brain. Postmortem analyses showed that it had accumulated in the nasal cavity, in nerves in the throat, and in the gut of deceased Parkinson’s patients. Braak’s postmortem observations also showed that aggregations of the protein appeared in the vagus nerve—a superhighway of nerve-fiber bundles running between the brain and various organs of the body, including the heart, lungs, and gut. He concluded that some type of pathogen causing the neuronal cell damage seen in Parkinson’s could invade through the nose or gut and then travel up to the brain via the vagus nerve.

Researchers then started to wonder if aggregates of α-synuclein might travel through the body in a similar way—and studies have shown that it can. In 2014, Stellan Holmqvist, then at Lund University in Sweden, and colleagues showed that if they injected α-synuclein into the guts of rats, the protein could travel up the vagus nerve to their brains. And this June, Johns Hopkins University neuroscientist Ted Dawson and an international team of researchers showed that the fibrillar, pathological form of the protein can travel in a similar way in mice and lead to Parkinson’s-like symptoms in the rodents. “Not only do the mice have the motor features of Parkinson’s, they also have the nonmotor features,” Dawson told The Scientist at the time. “They’ve got cognitive dysfunction, anxiety, depression, problems with smell—all symptoms seen in human patients with Parkinson’s.”

These studies led researchers to propose that Parkinson’s might start in the gut years before the disease manifested as neurodegeneration in the brain. Despite the growing popularity of this hypothesis, however, new work is challenging the idea. For example, according to one study, there is no change in the risk of the disease among patients who have had their vagal nerves cut to stop the development of gastric ulcers. Moreover, in a recent study of more than 2,000 Parkinson’s patients, only 0.05 percent had mutations in the SNCA gene, leaving scientists questioning how α-synuclein accumulates in the other 99.95 percent of cases, and therefore if the protein is, in fact, at the root of Parkinson’s disease.

DISEASED CELLS

In the neurons of Parkinson’s patients, something appears to have gone wrong with the cellular waste-clearing processes. Reactive oxygen species (ROS) released from mitochondria may play a role, damaging lysosomes. If the lysosomes don’t function properly, then cellular waste products are left in the cell to accumulate.

HEALTHY CELLS

Unneeded proteins, lipids, and other cellular materials are typically gathered into vacuoles, which fuse with lysosomes to clear the cells of the waste.